REMARKS

I. Status of the claims

Claims 1, 4-18, and 20-22 are pending. Claim 2 has been canceled without prejudice or disclaimer. Claims 3 and 19 were previously canceled. Of course, Applicant reserves the right to file one or more continuing applications to the canceled subject matter. Claims 21 and 22 have been added. Claims 1 and 4-18 have been amended. Claims 4-6, 8, 9, and 10-18 have been amended purely for grammatical reasons. Other claims have been amended for the reasons that follow.

Claim 1 has been amended to better clarify the constituents that make up the claimed adjuvant composition. Specifically, claim 1 recites an adjuvant composition that comprises (A) an ionic polysaccharide and (B) an immunostimulating complex. Precisely, the immunostimulating complex comprises a (i) saponin and (ii) a sterol. This amendment is fully supported by the originally-filed application. See, for instance, page 5, line 24 to page 6, line 29.

Claim 7 has been amended to qualify the saponin of claim 1 as "Quil A" and the sterol of claim 1 as "cholesterol." This amendment is fully supported by the originally-filed application. See, for instance, page 10, lines 11-15.

Claims 21 and 22 have been amended to recite the alternative optional qualifier of original claim 17, *i.e.*, the composition further comprises a "pharmaceutically acceptable diluent."

Since none of these amendments introduce new matter, Applicant respectfully requests their entry.

II. Summary of the Office Action

i. Claims 1-2, 4-18, and 20 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Examiner "fails to comprehend how applicant considers that the saponin component (Quil A) could comprise both itself and a 'sterol' (cholesterol), since these two entities have been listed as separate components." Office Action at page 2.

ii. Claims 1-2, 4-18, and 20 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner states that he has "failed to find any description at page 10 [of the specification] for the 'sterol' component (cholesterol) being considered as a part of the 'saponin' component." Office Action at page 3.

iii. Claims 1-2, 4-7, 13-14, and 17-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over James *et al.* (WO 88/07547) or Moss *et al.* (WO 91/04052) in view of MacKenzie *et al.*, (U.S. 4,981,684).

iv. Claim 15 is rejected under 35 U.S.C. § 103(a) as being unpatentable over James *et al.* or Moss *et al.*, either in view of MacKenzie, and further in view of McNamara (WO 99/02180).

III. Applicants' response overcomes the Office's rejections

i. Claim 1 has been amended to clarify the relationship between the saponin and sterol components of the claimed adjuvant composition and is, therefore, not indefinite

Claims 1-2, 4-18, and 20 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicant has now rephrased claim 1 to better clarify Applicant's claimed invention, namely an adjuvant composition that comprises (A) an ionic polysaccharide and (B) an immunostimulating complex. It is the immunostimulating complex that comprises a (i) saponin and (ii) a sterol. For this reason, Applicant also has canceled claim 2, which Applicant had previously used to characterize the "saponin component" of claim 1 as "an immunostimulating complex."

The present adjuvant composition is supported by the entire originally-filed specification. See, for instance, page 9, lines 19-29, which states that the "saponin component" is preferably "in the form of an immunostimulating complex." See also pages 10 and 11, which disclose the constituents of the immunostimulating complex and the claimed adjuvant composition.

Since the application fully supports the composition recited in claim 1, Applicant's amendment introduces no new matter into claim 1 and is, therefore, free from objection. Accordingly, Applicant respectfully requests that the Examiner withdraw these rejections.

ii. Prior to the effective filing date of the present application, the skilled artisan was well aware of the conventional wisdom which taught that a variety of sterols, not only cholesterol, could be used to formulate an immunostimulating complex, such as an ISCOM

The Examiner rejected claims 1-2, 4-18, and 20 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner states that "the single disclosed species of cholesterol utterly fails to support recitation of the new genus of 'sterols'." Office Action at page 3.

Applicants disagree. As explained in this section, the skilled artisan, after having read the present specification, would have immediately have understood that Applicants possessed the claimed genus of sterols in an immunostimulating complex. The present application accommodates the replacement of "one or more" components of the inventive immunostimulating complex with "a functional equivalent" (page 10, lines 15-17). Accordingly, the skilled artisan would have understood, before the present invention was made, that alternative sterols, not only cholesterol, could be incorporated into an immunostimulating complex.

Indeed, as early as 1987, Morein taught that various "steroids, such as cholesterol, cholestanol, caprostanol, phytosterols, *e.g.*, stigmasteroll sitosterol, mycosterols, *e.g.*, ergosterol," could be used to prepare immune stimulating complexes. See page 5, lines 32-34 of WO 87/02250 (appended), which published on April 23, 1987, and column 3, lines

41-46 of the U.S. counterpart, U.S. Patent No. 5,254,339 ("*Process for preparing immune complexes*"), which issued on October 19, 1993 (appended).

Similarly, in 1990, De Vries *et al.* taught that "the known sterols of animal or vegetable origin, such as cholesterol, lanosterol, lumisterol, stigmasterol and sitosterol," could be used to make an ISCOM. See column 2, lines 51-54 of U.S. Patent No. 4,900,549 (appended) ("*Process for preparing immunogenic complexes and pharmaceutical composition containing these complexes*"), which issued on February 13, 1990. In the same way, Garcon *et al.* in 1996 described a vaccine formulation in which "well known" sterols, including "β-sitosterol, stigmasterol, ergosterol, ergocalciferol, and cholesterol" could be used to produce the vaccine composition. See page 1, lines 17-22 of WO 96/33739 (appended).

Hence, the conventional wisdom taught the fungibility of various sterols in an immunostimulating complex, ISCOM. After reading the present application, which teaches that an ISCOM's cholesterol can be replaced with a "functional equivalent," the artisan would know, therefore, that any one of a number of sterol species could be incorporated into Applicant's claimed adjuvant composition.

With respect to literal support for the genus "sterol" by Applicant's disclosure of "cholesterol," Applicant points to the MPEP, which states that "there may be situations where one species adequately supports a genus" (MPEP section 2163). For instance, in *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979), the court held that disclosure of corticosteroid in DMSO was sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid." Hence, the court concluded that "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds."

Furthermore, the MPEP notes that a satisfactory disclosure of a genus depends on whether one of skill in the art would recognize that the applicant was "in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed" (MPEP 2163). In view of the state of the ISCOM-

related art prior to the present invention, therefore, the skilled person would recognize that Applicant's disclosure of "cholesterol" indeed does provide such satisfactory written description for the "sterol" genus.

For at least these reasons, Applicant believes that the term "sterol" is fully described by the specification and respectfully requests that the Examiner withdraw this rejection.

iii. There was no motivation to combine the cited prior art because none of the references recognised the undesirable reactogenic effects that ionic polysaccharides have on the recipient and they, therefore, do not describe a composition for inducing high adjuvant activity with low reactogenicity

The Examiner rejected claims 1-2, 4-7, 13-14, and 17-18 under 35 U.S.C. § 103(a) as allegedly unpatentable over James *et al.* (WO 88/07547) or Moss *et al.* (WO 91/04052) in view of MacKenzie *et al.*, (U.S. 4,981,684). The Examiner also rejected claim 15 as allegedly unpatentable over James *et al.* or Moss *et al.*, either in view of MacKenzie, and further in view of McNamara (WO 99/02180).

The skilled artisan would not have been motivated to combine the cited prior art, however, because none of the primary references recognised or addressed the undesirable reactogenic effects that ionic polysaccharides have on a recipient, when those polysaccharides are used as adjuvants.

To elaborate, DEAE-dextran is known in the art to be a very strong adjuvant, but one that often induces unacceptable reactogenicity. The present application addresses and solves this problem. The adjuvant composition of the present invention combines ionic polysaccharides, such as DEAE-dextran, with an immunostimulating complex, which comprises a saponin and a sterol, which is a composition that Applicant found to "maintain the adjuvant activity of both components, particularly of the more powerful adjuvant DEAE-dextran, but also of immunostimulating complexes."

The benefit of this combination is that "the unwanted reactogenicity of the DEAE-dextran is neutralised." See page 11, lines 20-29 of the present specification. Thus, the fact that this combination maintains adjuvant activity without the unwanted reactogenicity of DEAE-dextran was unexpected, since it was expected that combinations of reagents would be

more reactogenic than the individual components (see page 11, lines 28-29 of the specification).

Furthermore, as disclosed in the present specification at page 5 line 28 to page 6 line 6, the adjuvant composition of the present invention has been found to have high adjuvant activity combined with low reactogenicity, which provides an advantage over other known adjuvants in possessing an unusual combination of properties as set out at page 6 lines 1-6, namely:

a) an ability to elicit a very strong immune response to a range of antigens;

b) exhibit low reactogenecity or reactivity;

c) exhibit a reactogenecity that is lower than that of the more reactogenic components of the combination;

d) the adjuvant effect or immunostimulating effect is greater than that generated by the individual components alone.

As pointed out in the previous response, James *et al.* does not disclose or teach the inclusion of a sterol in the adjuvant, nor the replacement of the saponin with an immunostimulating complex, which itself comprises a saponin and a sterol. In particular, James *et al.* does not address the problem of unacceptable reactogenicity arising from the use of DEAE-dextran as an adjuvant and, therefore, does not provide any motivation which would lead the skilled person to replace the saponin in the adjuvant of James *et al.* with an immunostimulating complex as now recited in claim 1.

This lack of motivation is further evidenced by the fact that in the art it was expected that combinations of adjuvants would be more reactogenic than the individual components, so it would not have been obvious to a person skilled in the art that replacement of the saponin in the adjuvant of James *et al.* with an immunostimulating complex as taught by the present inventors would result in a combination where the unwanted reactogenicity of the DEAE-dextran is neutralised while still maintaining the adjuvant activity of both components.

Furthermore, MacKenzie *et al.* is silent on the issue of dose-site reactogenicity. Accordingly, the person skilled in the art would have no reason to conclude that the reactogenicity of a vaccine composition, which includes DEAE-dextran as an adjuvant, could be substantially neutralised by the claimed combination of elements.

There also would have been no motivation to combine the teachings of MacKenzie *et al.* and Moss *et al.*, because Moss *et al.* is directed to an implantable solid vaccine, which comprises (1) an antigenic substance, (2) an ionic polysaccharide, such as DEAE-dextran, (3) a saponin, and (4) large amounts of cholesterol (for example, 10-80% of the final formulation –see Figure 2) as a *filler* for the solid composition. Moss *et al.* does not recognise or address the problem of dose-site reactogenicity of DEAE-dextran when used as an adjuvant and there is no motivation to replace the saponin with an immunostimulating complex as taught by MacKenzie.

Furthermore, it will be apparent from the present specification that the adjuvant composition of the present invention is a composition which can be administered as a liquid, with the composition maintaining the adjuvant activity of the components whilst the reactogenicity is essentially eliminated. Moss *et al.* contains no disclosure or teaching in relation to dose-site reactogenicity arising from the use of DEAE-dextran in the adjuvant, and accordingly it provides no motivation to a person skilled in the art to change the adjuvant composition as described by the Examiner in order to address this problem. Once again, as noted above, MacKenzie *et al.* contains no discussion on dose-site reactogenicity, so it would not motivate a person skilled in the art to replace the saponin in the adjuvant composition of Moss *et al.* in order to decrease that reactogenicity, even if dose-site reactogenicity of DEAE-dextran had been identified by Moss *et al.* as a problem.

Moss *et al.* suggests that the presence of cholesterol in the formulated implants "has the added advantage of reducing the toxicity of the saponin," but says nothing about countering the dose-site reactogenicity that is induced by DEAE-dextran. Moreover, Moss *et al.* does not disclose or suggest the use of an immunostimulating complex. Thus, Moss *et al.* would not have motivated a person skilled in the art to address the problem of reactogenicity of DEAE-dextran by combining that ionic polysaccharide with an

immunostimulating complex in order to neutralise the reactogenicity of the DEAE-dextran, particularly where it was expected in the art that combinations of adjuvants will be more reactogenic than the individual components (see page 11 lines 28-29).

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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